REMARKS

Status of the claims

Claims 23, 28-30, 36 and 50-57 are in the application. Claims 23, 28-30, 36 and 50-57 have been rejected. By way of this amendment, claims 23, 29 and 30 have been amended and new claims 58-80 have been added. Upon entry of the amendment, claims 23, 28-30, 36 and 50-80 will be pending.

Summary of the Amendment

Claim 23 has been amended to more clearly set forth the nature of the active agent. Support for the amendment is found throughout the specification, particularly page 7. No new matter has been added.

Claim 29 has been amended to more clearly set forth the nature of the active agent. Support for the amendment is found throughout the specification particularly page 22. No new matter has been added.

Claim 30 has been amended to change its dependency and to correct an obvious error. Support for the amendment is found throughout the specification particularly page 27. No new matter has been added.

New claims 58-80 have been added to claim specific embodiments of the invention. Support for new claims 58-80 is found throughout the specification. No new matter has been added.

No new matter has been added by these amendments.

Objection to Claim 29

Claims 29 is objected to as being in improper dependent form and failing to further limit the subject matter of Claim 23. In view of the amendment to claims 23 and 29, the objection is moot.

Rejection under 35 U.S.C. §112, first paragraph

Claims 23, 28-30, 36 and 50-57 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way to enable one of ordinary skill in the art, to which it pertains or to which it is most nearly connected, to make and/or use the invention.

The Official Action states that

> applicant's amendment and response fails to discuss how the *claimed* invention overcomes and does not parallel the inherent difficulties one skilled in the art would face with administering the claimed antibodies. As set forth previously, these burdens include impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets, insufficient target specificity and induction of HAMA.

Applicants respectfully urge that one skilled in the art would accept Applicants' assertion of enablement. Applicants respectfully urge those skilled in the art would accept that the claimed invention is operable despite references in the past which describe the various technical issues which arise in developing an antibody therapeutic.

Since the Examiner's position is predicated around predictability in the art, the question of what was known at the time of the invention to those skilled in the art provides evidence as to the question of predictability. In re Marzocchi, 439 F.2d 220, 223-224, 169 USPQ 367, 369-370. A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which are relied upon for enabling support. In re Wright 999 F.2d 1557, 1562, 27 USPQ2d 1510. 1513 (Fed. Cir. 1993). Thus, an overview of the state of development of anticancer therapy based on systemic administration of antibodies at the time of the invention is relevant and determinative to the question of the general state of knowledge to those skilled in the art or cancer immunology.

References Jain, Dillman and Weiner are cited in the Official Action as evidence of unpredictability in support of the assertion of non-enablement. Neither Jain nor Dillman nor Weiner provide sufficient evidence that one skilled in the art would doubt the objective truth of Applicant's assertion that the claimed invention is enabled.

Jain and Dillman are cited as pointing out problems and obstacles in developing antibody based therapeutics. Both references also discuss the promise of antibody-based therapeutic. Applicants urge that Weiner dispels any doubts suggested by Jain or Dillman and puts in proper context the issues raised in those references. Weiner provides strong evidence that those having ordinary skill in the art would accept Applicant's assertion of enablement. For example, Weiner's abstract states:

> Monoclonal antibody-based therapeutics are beginning to realize the promise that was predicted with the advent of the core technology more than 20 years ago.

Weiner states in the last sentence of the full paragraph on the right column of page 41 that prior evaluations reached

> the premature and unwarranted conclusion that antibody-based therapeutics do not show sufficient promise to be considered cutting-edge and valuable

In the first complete sentence on page 42, Weiner states that

> [e]ncouraging clinical results will be described in which antibodies are used to... .... (4) deliver radionuclides, toxins and chemotherapeutic agents.

On page 43, in the first paragraph of the section entitled "Factors regulating antibody based tumor targeting" Weiner states that

> [i]t should be emphasized that the identification of obstacles is not a reason for discouragement

indicating that such obstacles are merely part of the development process. Weiner states in the right column on page 43 that

> it can be anticipated that in patients with large tumors, therapy using MoAb will be compromised.

It is clear from this statement that while Weiner does not say that MoAbs are completely useless in treating patients with antibodies, he does clearly imply that antibodies are useful in the treatment of patients with tumors that are not large.

Weiner provides evidence that those skilled in the art would believe the objective truth of Applicant's assertion that the claimed invention is enabled. Weiner also discusses on page 48 drug immuno-conjugates, such as those used in the claimed invention, as an improvement over conventional chemotherapy. The summary on page 49 refers to the development of clinical uses of antibodies offers and the promise and expectations that those of having ordinary skill in the art have.

A significant issue raised by the Examiner in citing Weiner was the requirement for specificity of an antibody-based therapeutic. The claims have been amended to refer to metastatic colorectal cancer. As discussed in the specification, the ST receptors which are targeted are not normally expressed outside of the intestine/colon. Further, as pointed out in the specification, the interior of the intestine/colon is tightly walled off form the inside of the body and vice versa. (Page 10 of the specification) Thus, administration of the compositions will not interact with normal colon tissue that expresses the receptor. The concern outlined by Weiner and the Examiner has thus been addressed by the amendment.

Evidence from clinical and preclinical trial data provided to the Food and Drug Administration has been used in submissions the USPTO as an indication of the state of enablement in the art (MPEP 2164.05) even though the standards for FDA approval far exceed those required for patentability. Studies of toxicity, pharmacokinetics and biodistribution are each routinely required during the approval process for medications, such as oncologic drugs. Pharmacokinetic and biodistribution data are especially germane to the areas of the Examiner's stated areas of difficulty relating to trafficking, availability and accessibility of targets and antigenic heterogeneity; the phenomenon of HAMA is applicable to and addressed in toxicity testing.

At the present time numerous monoclonal antibody preparations have been approved for therapeutic use by the United States FDA:

Trade name	Manufacturer	Target	Origin	Indication
Orthoclone	J&J	CD-3	all rodent	transplantation rejection
ReoPro	Centocor/Lilly	GPIIb, IIIa	chimeric	High risk angioplasty
Rituxan	IDEC/Genentech	CD20	chimeric	Non-Hodgkin's lymphoma
Remicade	Centocor	TNF	chimeric	Crohn's disease
Simulect	Novartis	CD25	chimeric	Transplantation rejection
Synagis	Medimmune	RSV F Protein	humanized	RSV infection
Zenapax	PDL/Roche	CD25	humanized	Transplantation rejection
Herceptin	Genentech	HER-2	humanized	Breast cancer
Mylotarg	Wyeth	CD33	humanized	Acute myelogenous leukemia (AML)
Campath	Berlex	CD52	humanized	Chronic lymphocytic leukemia (CLL)
Zevalin	BiogenIdec	CD20	mouse	Non-Hodgkin's lymphoma
Bexxar	GSK/Corixa	CD20	mouse	Non-Hodgkin's lymphoma
Avastin	Genentech	VEGF	humanized	Colon Cancer
Erbitux	Imclone/BMS	EGFR	humanized	Colon cancer

Also, Panorex, a murine monoclonal antibody, is approved in Germany for the treatment of colon cancer.

Trade name	Manufacturer	Target	Origin	Indication
Panorex	GSK	EGP-2	all rodent	colon carcinoma

The standard for enablement is not whether all potential obstacles to clinical efficacy can be circumvented without complication or side effect, but whether the claimed invention can be described in such a manner as to enable a skilled practitioner to achieve the disclosed result. In the instant case, that result involves the binding of the claimed antibodies to cancer targets within an individual with a particular type of metastatic cancer which cells have a binding affinity for said antibodies. Contemporaneous with the time of the invention, the state of knowledge of those skilled in the art would have been sufficient to predict this theoretical level of efficacy, given the disclosure in the specification in combination with the results already in the domain of the practitioners.

While it was recognized early in the clinical development of therapeutic monoclonal antibodies that antibodies derived from mice or other non-human animals were themselves antigenic and elicited immune responses in human tissue, this factor in itself did not cause the mice antibodies to be nonfunctional for their intended purposes. An illustrative example of this point is the therapeutic antibody, OKT-3, sometimes known also as orthoclone or muromonab-CD3. This mouse monoclonal antibody was thoroughly investigated by FDA procedures for toxicology as detailed in the National Institute of Health (US), National Cancer Institute, Common Toxicity Criteria, Bethesda, MD. The labeling insert and toxicity warnings for this drug can be found at www.orthobiotech.com/orthoclone.html. This particular antibody is primarily used in connection with inhibition of tissue rejection in transplantation procedures, but the warnings of the clinical side effects of HAMA including increased incidence of anaphylaxis might apply to any antibody similarly administered. These side effects are no more indicative of a lack of operability of the antibody for its intended purpose than that nausea and hair loss indicate therapeutic ineffectiveness of chemical chemotherapeutic drugs. In short, induction of HAMA is a problem to be dealt with by medical procedures or further research, not a factor bearing upon operability of the claimed invention or inadequate enablement in the disclosure of how to use the antibodies.

The Weiner reference, cited by the Examiner in the first Office Action (Seminars Oncology (1999) 26:41-50) did point in Table 2 thereof several obstacles to be overcome in order to maximize clinical effectiveness of antibody therapy in cancer treatment. As noted above however, the author suggests that the presence of these obstacles is "not a reason for discouragement", and that "properly exploited, the [binding to tumor antigens] of MoAb and their derivatives led to some striking examples of antitumor effects". Writing on drug immunoconjugates, and radioimmunoconjugates, the author states that, "early studies of RIT have shown that partial short-lived clinical responses can be achieved in some patients with advanced solid tumors", and concludes with statements that overall results are "promising" and "are expected to add to the list of novel agents available for the treatment of malignancies....". Since the criteria for enablement is not the achievement of perfect therapeutic indicia free of side effects and complications, this reference serves to illustrate

that treatments with the antibodies of the invention would be predictively operative to a degree that can be measured in clinical studies. This is the test for an adequate disclosure of how to make and use the claimed invention.

The Dillman reference, also cited by the Examiner in the first Office Action (Annals of Internal Medicine (1989) 111:592-603), is relevant to the state of knowledge of those of skill in the art at a time prior to the invention, since it was published before the application was filed. The abstract of the reference states only that factors of tumor cell heterogeneity and lack of cytoxicity *"have limited clinical efficiency"*. It should be noted that this statement immediately follows a statement that *"trials of antibody alone and radiolabeled antibodies have confirmed the feasibility of this approach...."* Again it should be emphasized that the standard for enablement of the disclosure is not that the claimed invention's usefulness is without practical limitation, but that the teachings provide guidance to the practitioner skilled in the art on how to make and use the invention. Thus the statement on the technique of antibody therapy shows that the cancer immunotherapy community as of 1989 believed that antibody therapy was "feasible and promising" as a therapeutic modality. This author concludes that "the rationale for the use of antibodies alone or as carriers of cytotoxic agents is sound, and some of some of these agents are impressive in vitro and in animal models." Soundness of a hypothesis is hardly a corollary of unpredictable results.

Finally the holding from In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) is applicable here since in that case the court found that for the making of monoclonal antibodies all the methods needed to practice the invention were well known and that the level of skill in the art for the theoretical use of monoclonal antibodies based on their demonstrated specificities against isolated antigens in vitro were enabled. It would be predictive that if a given antibody is reactive with a given isolated antigen, it will also bind to that antigen in vivo, and that experimentation to determine whether this hypothesis works in vivo is the essence of the clinical trial and not "undue". Other antibodies to tumor antigens produced under analogous research to that described in the specification have

achieved and exceeded this criterion. Thus, the teaching in the present invention is not unpredictable

It is noteworthy that in their recent opinion Chiron Corp. v. Genentech, Inc., 363 F.3d 1247 (Fed. Cir. 2004), the Court of Appeals discussed murine antibodies and stated that

> As noted, murine antibodies play an important role in these technologies. While useful for diagnostics and short-term therapies, murine antibodies cannot be administered to people long-term without increasing the risk of a deleterious immunogenic response. This response, called Human Anti-Mouse Antibody (HAMA), occurs when a human immune system recognizes the murine antibody as foreign and attacks it. A HAMA response can cause toxic shock or even death.

The Court clearly acknowledges that murine antibodies are useful for short-term therapies and can only be used in long-term therapies with a significant risk of a deleterious immunogenic response. Clearly the Court accepted the use of murine antibodies as therapeutics, particularly those administered short-term. In pointing out the problems with long-term use, the Court clearly stated that the problem was the risk of HAMA. Risk and the attendant risk benefit analysis associated with using a therapeutic are issues for the FDA to weigh in determining whether or not a therapeutic is safe enough to be marketed. The standards used by the patent office are different and only require that an invention is enabled, not whether its benefits outweigh risks to safety in order for the invention to be used.

The claimed invention is enabled. When all of the evidence is viewed in its totality one skilled in the art would accept the object truth of Applicant's assertion of enablement. Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Non-statutory Double Patenting

Claims 23, 28-30, 36 and 50-57 are rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over 1, 5, 9-10, 30, 31, 55, 56 and 58 of U.S. Patent No. 5,879,656. As noted earlier, once claims have been indicated to be allowable, Applicants shall promptly provide Terminal Disclaimer as

appropriate. To that end, the Examiner is invited to contact Applicants' undersigned representative and inform him of the allowability of the claims so that a Terminal Disclaimer can be promptly filed by telefax.

Conclusion

For the foregoing reasons, claims 23, 28-30, 36 and 50-80 are in condition for allowance. A notice of allowance is earnestly solicited.

Respectfully submitted,

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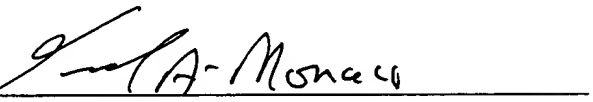
BY 

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